Remarks

Amendments

Claim 7 has been amended to correct a typographical error. The amendment is not a narrowing amendment and adds no new matter. Applicants respectfully request the entry of the amendment to claim 7.

Objection to Claim 7

Claim 7 has been "objected to" for a typographical error. Claim 7 has been amended to correct the error. Applicants respectfully request withdrawal of the objection.

Rejection of Claims 1-5, 7-10, 18 and 19 Under 35 U.S.C. § 101

Claims 1-5, 7-10, 18 and 19 stand as rejected under 35 U.S.C. § 101 as allegedly directed to non-statutory subject matter. Applicants respectfully traverse the rejection.

The USPTO has issued "Interim Guidance for Determining Subject Matter Eligibility for Process Claims" (75 Fed. Reg. 43922 (Jul. 27, 2010)) ("the Guidance") in response to the decision by the Supreme Court in *Bilski v. Kappos,* 130 S. Ct. 3218 (2010). 35 U.S.C. § 101 has broad patent-eligibility principles, however, the Supreme Court has identified three specific exceptions to patentability: laws of nature, physical phenomenon, and abstract ideas. *Bilski,* 130 S. Ct. at 3225. However, "an *application* of a law of nature or mathematical formula to a known structure or process may well be deserving of patent protection." *Bilski*, 130 S. Ct. at 3230 (emphasis in original) (citing *Diamond v. Diehr,* 101 S.Ct. 1048 (1981)). The instantly claimed methods comprise patent eligible subject matter because they do not fall within the three exceptions noted by the Supreme Court and because, *inter alia*, they require the use of certain apparatuses and result in the transformation of matter. In the Guidance, a list of factors weighing toward patent eligibility were enumerated including:

- Recitation of a machine or transformation (either express or inherent).
- Machine or transformation is particular.
- Machine or transformation meaningfully limits the execution of the steps.

- Machine implements the claimed steps.
- The article being transformed is particular.
- The article undergoes a change in state or thing (e.g., objectively different function or use).
- The article being transformed is an object or substance.
- The claim is directed toward applying a law of nature.
- Law of nature is practically applied.
- The application of the law of nature meaningfully limits the execution of the steps.
- The claim is more than a mere statement of a concept.
- The claim describes a particular solution to a problem to be solved.
- The claim implements a concept in some tangible way.
- The performance of the steps is observable and verifiable.

See 75 Fed. Reg. at 43927.

Machine or Apparatus

The instantly claimed methods inherently require the use of standard laboratory apparatuses. For example, Figure 1 of the application shows an exemplary schematic of one embodiment of the invention depicting a syringe and Petri plates. The syringe can be used, for example, in "obtaining an antibody sample from one or more hosts" in claims 1, 18, and 19. The Petri plates, can be used, for example, in "probing an expression library of clones" of claims 1, 18, and 19. Of course, the steps of "adsorbing the antibody sample with cells or cellular extracts of the microbe or pathogen that have been grown *in vitro*" and "isolating unadsorbed antibodies" would require the use of standard laboratory equipment.

Transformation

The instant methods result in the transformation of several types of matter. Firstly, an antibody sample is absorbed with cells or cellular extracts of the microbe or pathogen that have been grown *in vitro* in step (b) of claims 1, 18, and 19. The antibody sample is transformed by this step because after the performance of the step the sample contains not just antibodies, but (1)

antibodies that are adsorbed to antigens of the cells or cellular extracts of the microbe or pathogen that have been grown *in vitro* and (2) antibodies that are not adsorbed to antigens of the cells or cellular extracts of the microbe or pathogen that have been grown *in vitro*.

Secondly, the unadsorped antibodies are isolated in step (c) of claims 1, 18 and 19. The sample is therefore transformed because antibodies that are adsorbed to antigens of the cells or cellular extracts of the microbe or pathogen that have been grown *in vitro* are removed from the sample, thereby further transforming the sample.

Thirdly, further transformation occurs in step (d) of the methods where expression libraries are probed and clones are isolated thereby transforming the expression library and the clones.

Applying a Law of Nature

The laws of nature are practically applied in the methods of the invention by manipulating the fact that (1) certain antibodies are produced by hosts in response to infection and that (2) microbes express certain antigens only *in vivo* when they are actively causing infection in a host and not when they are grown *in vitro* in the laboratory. The methods of the invention identify these certain antigens.

Concepts and Performance

The claims describe a particular solution to a problem to be solved. That is, the claimed methods result in the isolation a polypeptide that is expressed by a microbe or pathogen only while the pathogen is causing infection *in vivo*. This is important because it is unlikely that all regulated virulence determinants of a pathogen can be identified *in vitro* because it is technically impossible to determine and mimic all of the complex and changing environmental stimuli that occur at the site of an infection. *See* specification at page 1, line 21 to page 2, line 1.

The claims implement this concept in a tangible way. That is, the methods result in the isolation of a particular polynucleotide that is expressed by a microbe or pathogen only while the microbe is causing infection *in vivo*.

The performance of the steps of the methods of the invention is observable and verifiable. That is, the methods result in the isolation of a particular polynucleotide that is expressed by a microbe or pathogen only while the microbe is causing infection *in vivo*. Furthermore, the invention provides methods for confirming that the isolated polynucleotide is expressed only *in vivo*. *See* withdrawn claim 6.

The claims of the invention are clearly drawn to patent eligible subject matter under 35 U.S.C. § 101 because, *inter alia,* particular apparatuses are used to perform the methods of the invention, transformation of matter occurs during the performance of the methods, laws of nature are practically applied, the methods describe a particular solution to a problem to be solved, the methods implement a concept in a tangible way, and the performance of the steps is observable and verifiable. Applicants respectfully request withdrawal of the rejection.

Rejection of Claims 1-5, 7-10, 18 and 19 Under 35 U.S.C. § 112, first paragraph

Claims 1-5, 7-10, 18 and 19 stand as rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking written description. Applicants respectfully traverse the rejection.

The Office asserts that the specification does not support the claim language "obtaining an antibody sample from one or more hosts infected with the microbe or pathogen." The specification, however, teaches:

> Briefly, the methods, termed *in vivo* induced antigen technologies (IVIAT), comprise obtaining a sample of antibodies against antigens that are expressed by the microbe *in vivo* and *in vitro* and adsorbing these antibodies with cells or cellular extracts of the microbe that have been grown *in vitro*. An example of a sample of antibodies that can be used in the invention is sera from patients who have been or are infected with the microbe. *See, e.g.* Figure 1.

See specification page 10, lines 10-15. Therefore, the specification clearly provides support for this claim language. Applicants respectfully request withdrawal of the rejection.

Rejection of Claims 18 and 19 Under 35 U.S.C. § 112, first paragraph

Claims 18-19 stand as rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement. Applicants respectfully traverse the rejection.

Under 35 U.S.C. § 112, all that is required for enablement is that the specification describe the invention in such terms as to enable a person skilled in the art to make and use the invention. The test of enablement is whether one reasonably skilled in the art (1) could make and use the invention (2) from the disclosures in the patent coupled with information known in the art (3) without undue experimentation. *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988); *United States v. Telectronics, Inc.*, 857 F.2d 778 (Fed. Cir. 1988); M.P.E.P. § 2164.01. Applicants submit that it is a matter of routine experimentation to use the methods of the invention to isolate polynucleotides, vaccine targets, and diagnostic targets. The law clearly states that "a considerable amount of experimentation is permissible, if it is merely routine." *In re Wands,* 858 F.3d 731, 737 (Fed. Cir. 1988). Furthermore, the fact that experimentation may be complex does not necessarily make it undue. *Massachusetts Institute of Technology v. A.B. Fortia,* 774 F.2d 1104 (Fed. Cir. 1985); *In re Wands,* 858 F.2d at 737 (Fed. Cir. 1988). Thus, the test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *In re Angstadt*, 537 F.2d 498 (CCPA 1976).

The Office asserts that the claim scope is unduly broad with respect to the encompassed host, microbe, pathogen, antibody, antigen, vaccine and diagnostic target.

I. Host, Microbe, Pathogen, Antibody, and Antigens

The invention provides methods of screening for isolating a polynucleotide from a microbe or pathogen that is expressed in a host only *in vivo*. Applicants must therefore, teach how to make and use the screening method. The

specification teaches that the host can be any kind of animal including humans. *See* specification, page 11, line 19. One of skill in the art could easily obtain an antibody sample from any host. The specification teaches that the microbe or pathogen can be "any kind of a bacterium, a virus, a parasite, a prion, or a fungus." *See* page 11, lines 22-23. One of skill in the art could identify and obtain an antibody sample from a host infected with any kind of microbe or pathogen. The specification teaches that the antibody sample can be adsorbed with cells or cellular extracts of the microbe or pathogen that have been grown *in vitro*. *See* specification, page 12, lines 14-21. One of skill in the art could make cells or cellular extracts of the microbe or pathogen that have been grown *in vitro* and would know how to do an adsorbtion step.

Furthermore, the specification provides a working example of the successful use of the screening methods of the invention. *See* Examples 1-5. Additionally, the IVIAT methods of the invention have been used by the those of skill in the art to isolate polynucleotides of microbes including, *e.g., Vibrio anguillarum, Porphyromonas gingivalis, Streptococcus suis, Brucella abortus, Salmonella enterica, Edwardsiella tarda, Paracoccidiodes brasileinsis, Borrelia burgdorferi, Mycobacterium tuberculosis, Bacillus anthrasis, Tannerella forsythia,* group A *Streptococcus, Escherichia coli, Actinobacillus actinomycetemcomitans, Vibrio vulnificus, Vibrio choerae*. *See* Declaration of Dr. Handfield under 37 C.F.R. § 1.132, ¶ 3, filed herewith. These polynucleotides are expressed by a microbe only *in vivo* as taught by the instant specification.

Therefore, one of skill in the art could make and use (and have made and used) the methods of the invention to identify polynucleotides expressed by microbes only *in vivo*.

II. Vaccine Targets and Diagnostic Targets

The Office asserts that that the specification does not provide enablement for methods of obtaining a vaccine or diagnostic target. Applicants note that the claims recite methods of obtaining a "vaccine target," not a "vaccine." Vaccine targets are known to those of skill in the art as candidate polynucleotides or polypeptide antigens expressed from the polynucleotides that have a potential to

be useful as a vaccine. *See* Declaration of Dr. Handfield, ¶ 7. Diagnostic targets are known to those of skill in the art as candidate polynucleotides or polypeptide antigens expressed from the polynucleotides that have a potential to be useful as a diagnostic composition. *See* Declaration of Dr. Handfield, ¶ 7.

Those of skill in the art have recognized that the IVIAT methodology of the instant invention is useful to identify vaccine targets or candidates and diagnostic targets or candidates. *See* Declaration of Dr. Handfield, ¶ 4. The specification terms the methods of the invention as "IVIAT methodology." *See* specification page 10, lines 10-15. The term "IVIAT methodology" has also been recognized in the art as the name of methods as described in the instant invention. *See* Declaration of Dr. Handfield, ¶ 2. Over 20 scientific papers have been published that report the successful use of the IVIAT methodology of the claims to isolate polynucleotides of microbes that are expressed only *in vivo*. In particular, those of skill in the art have recognized that polynucleotides and the polypeptides expressed from the polynucleotides identified by IVIAT are important vaccine targets and diagnostic targets, just as described by the specification. *See* Declaration of Dr. Handfield, ¶ 4.

For example, Gu *et al.* teaches that the "the proteins identified using IVIAT may be useful potential vaccine candidates or virulence markers." *See* Gu *et al.* Use of *in vivo*-induced antigen technology (IVIAT) for the identification of *Streptococcus suis* serotype 2 *in vivo*-induced bacterial protein antigens. BMC Microbiol. 9:201 (copy of abstract attached). Kudva *et al.* teaches that "Because ivi[at] proteins are expressed in response to specific cues during infection and might help pathogens adapt to and counter hostile *in vivo* environments, those identified in this study are potential targets for drug and vaccine development. Also, such proteins may be exploited as markers of O157 infection in stool specimens." Kudva *et al.*, Use of *in vivo*-induced antigen technology for identification of Escherichia coli O157:H7 proteins expressed during human infection. Infect Immun. 73:2665-79 (2005) (copy of abstract attached). Zou *et al.* teaches that "[t]he identification of ivi[at] genes in *V. anguillarum* M3 sheds light on understanding the bacterial pathogenesis and provides novel targets for the

development of new vaccines and diagnostic reagents." Zou *et al.*, Screening of genes expressed *in vivo* after infection by *Vibrio anguillarum* M3. Lett Appl Microbiol. 2010 Aug 26 (copy of abstract attached). Hu *et al.* teaches that "[a]ntigens identified in this [IVIAT] study are potential targets for drug and vaccine development and may be utilized as diagnostic agents." Hu *et al.*, Identification of *in vivo* induced protein antigens of *Salmonella enterica* serovar Typhi during human infection. Sci China C Life Sci. (2009) 52:942-8 (copy of abstract attached). Jiao *et al.* teaches that "these results demonstrate that Eta21 [an IVIAT protein], especially that delivered by DH5alpha/pTAET21, is an effective vaccine candidate against *E. tarda* infection." Jiao *et al.*, Identification and immunoprotective analysis of an *in vivo*-induced *Edwardsiella tarda* antigen. Fish Shellfish Immunol. (2009) 27(5):633-8 (copy of abstract attached). Song *et al.* teach that "IVIAT has proven useful in identifying previously unknown *in vivo*-induced genes that are likely involved in virulence and are thus excellent candidates for use in diagnostic, and therapeutic strategies, including vaccine design." Song *et al.* Genes of periodontopathogens expressed during human disease. Ann Periodontol. (2002) 7(1):38-42 (copy of abstract attached). *See* Declaration of Dr. Handfield, ¶ 5.

Therefore, those of skill in the art have recognized that polynucleotides and the polypeptides expressed from the polynucleotides that are discovered using the IVIAT methodologies of the invention are useful as vaccine targets and diagnostic targets. *See* Declaration of Dr. Handfield, ¶ 6.

Finally, the Office asserts that the working examples of the invention do not provide any information regarding vaccine development or use as diagnostic targets. This is incorrect because working Example 5 provides an example of the use of polypeptides identified using the methods of the invention as reagents to detect *A. actinomycetemcomitans* antibodies in periodontitis patients.

Those of skill in the art clearly recognize, as taught by the specification, that polynucleotides and the polypeptides expressed from the polynucleotides identified by the IVIAT methodologies of the invention are useful as vaccine

targets and diagnostic targets. Applicants respectfully request withdrawal of the rejection.

Rejection of Claims 1-5, 7, 8, 10, 18 and 19 Under 35 U.S.C. § 102(b)

Claims 1-5, 7, 8, 10, 18, and 19 stand as rejected under 35 U.S.C. § 102(b), as allegedly anticipated by Bickel *et al.* WO98/30910. Applicants respectfully traverse the rejection.

Anticipation under 35 U.S.C. § 102 requires the presence in a single prior art disclosure of each and every element of a claimed invention. *Lewmar Marine Inc. v. Barient Inc.*, 827 F2d 744, 747 (Fed. Cir. 1987).

Bickel does not teach or suggest "obtaining an antibody sample from one or more hosts infected with the microbe or pathogen." Rather, Bickel teaches that lab animals are immunized with proteins from a target cell. *See* Bickel page 5, lines 5-12; page 12, lines 24-28. The methods of the invention do not require the immunization of hosts with proteins from a target cell. Rather, hosts that have been infected with whole microbes or pathogens are used to obtain antibody samples.

The Office asserts that Bickel teaches methods comprising "obtaining an antibody sample from an immunized host (i.e., 'infected' with a microbe or pathogen, immunized with cells or cell fractions)." However, the immunization of lab animals with proteins from a target cell is not the same as "obtaining an antibody sample from one or more hosts infected with the microbe or pathogen." Immunization with proteins from a target cell is clearly not the same as infection with a microbe or pathogen.

Bickel does not teach or suggest each and every element of the instant claims. Applicants respectfully request withdrawal of the rejection.

Rejection of Claims 1-5, 7-10, 18, and 19 Under 35 U.S.C. § 102(b)

Claims 1-5, 7-10, 18, and 19 stand as rejected under 35 U.S.C. § 103(a), as allegedly obvious over Bickel *et al.* WO98/30910 and Suk *et al.* Applicants respectfully traverse the rejection.

As described above, Bickel does not teach or suggest "obtaining an antibody sample from one or more hosts infected with the microbe or pathogen."

Rather, Bickel teaches that lab animals are immunized with proteins from a target cell. *See* Bickel page 5, lines 5-12; page 12, lines 24-28. The methods of the invention do not require the immunization of hosts with proteins from a target cell. Rather, hosts that have been infected with whole microbes or pathogens are used to obtain antibody samples.

The Office asserts that Bickel teaches methods comprising "obtaining an antibody sample from an immunized host (i.e., 'infected' with a microbe or pathogen, immunized with cells or cell fractions)." However, the immunization of lab animals with proteins from a target cell is not the same as "obtaining an antibody sample from one or more hosts infected with the microbe or pathogen." Immunization with a proteins from a target cell is clearly not the same as infection with a microbe or pathogen.

If, as taught by Bickel, proteins from a target cell, such as a bacterium, were used to immunize a lab animal, then the target cell would necessarily be dead and non-infective. It would be impossible to then use the methods of Bickel to identify specific proteins that are expressed only when the bacterium is *in vivo* and causing infection in a host (as opposed to proteins that are expressed when the bacterium is growing *in vitro*). Therefore, Bickel does not teach or suggest the claims of the instant invention.

Suk does not cure the deficiencies of Bickel. Suk requires the use of two types of antibody populations (1) antibodies from animals immunized with killed cultured pathogens and (2) antibodies from infected hosts. Suk does not teach or suggest methods that require (1) antibodies from infected hosts and (2) cells or cellular extracts of the microbe or pathogen that have been grown *in vitro*.

Therefore, Suk and Bickel do not teach or suggest the methods of the invention and in particular do not teach or suggest obtaining an antibody sample from one or more hosts infected with the microbe or pathogen and adsorbing the antibody sample with cells or cellular extracts of the microbe or pathogen that have been grown *in vitro*. Applicants respectfully request withdrawal of the rejection.

Rejection of Claims 1-5, 7-10, 18 and 19 Under 35 U.S.C. § 112, first paragraph

Claims 1-5, 7-10, 18 and 19 stand as rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking written description. Applicants respectfully traverse the rejection.

Despite the fact that Applicants are claiming a screening methodology that can be used to identify specific polynucleotides of a microbe or pathogen, the Office claims that the written description is limited to only the specific polynucleotides of *A. actinomycetemcomitans* that are identified in the working examples of the specification. The Office appears to assert that methods of screening for particular polynucleotides or compounds only have written description when each and every polynucleotide or compound that might be discovered using the screening method is identified in the specification. This clearly is not the law. Rather, the standard for written description requires that a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. *See, e.g.*, *Moba, B.V. v. Diamond Automation, Inc.*, 325 F.3d 1306, 1319 (Fed. Cir. 2003); *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563 (Fed. Cir. 1991).

Applicants are not claiming the specific polynucleotides that can be discovered using the novel screening methods of the invention, rather, they are claiming methods of discovering the polynucleotides. Applicants must demonstrate possession of the claimed methods, not the polynucleotides that can be discovered using the methods.

The Office asserts that "regardless whether a compound is claimed *per se* or a method is claimed that entails the use of the compound, the inventor cannot lay claim to that subject matter unless he can provide a description of the compound sufficient to distinguish infringing compounds from non-infringing compounds, or infringing methods from non-infringing methods." This would be relevant case law if the Applicants were claiming the polynucleotides discovered by the screening methods of the invention or if the Applicants were claiming uses

of specific polynucleotides discovered by the screening methods of the invention. The Applicants, however, are claiming screening methods, not the actual polynucleotides that are discovered by use of the screening methods.

The claims have written description without the description of each and every polynucleotide that could be discovered using the screening methods of the invention. In holding otherwise, the Office would negate the patentability of all screening methods.

Finally, the specification provides working examples of the methods of the invention that can be applied to any microbe or pathogen. The Office has not provided reasoning or evidence to explain why the methods of the invention could not be applied to any microbe or pathogen. In fact, over 20 scientific, peer reviewed articles have been published extolling the uses and virtues of the IVIAT methodology as described in the specification. *See* Declaration of Dr. Handfield, ¶¶ 3-5. Therefore, given the specification, the working examples of the specification, and the fact that those of skill in the art have been able to replicate the methods of the invention in a plethora of microbes, one of skill in the art would have understood that the Applicants were in possession of the invention.

Rejection of Claims 1-5, 7-10, 18 and 19 Under 35 U.S.C. § 112, second paragraph

Claims 1-5, 7-10, 18 and 19 stand as rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. Applicants respectfully traverse the rejection.

A claim is definite when those skilled in the art would understand what is claimed when the claim is read in light of the specification. *See, Orthokinetics Inc. v. Safety Travel Chairs Inc.*, 806 F.2d 1565, 1576 (Fed. Cir. 1986). Claims must be sufficiently precise to permit a potential competitor to determine whether or not they are infringing. *See, Exxon Research and Eng'g Co. v. United States*, 265 F.3d 1371, 1376 (Fed. Cir. 2001).

The Office asserts that "potential method steps are present and it is not clear if these steps are required or not." The first issue mentioned by the Office is:

> After method step d, the statements "wherein a polynucleotide . . . is isolated" (claim 1), "wherein a vaccine target . . . is isolated" (claim 18), and "wherein a diagnostic target . . . is isolated" (claim 19) are present. However, it is not clear if this is a separate method step.

See Office Action page 18. One of skill in the art would understand that the when the clones are isolated from the expression library to which the unadsorbed antibodies bind, that the polynucleotide/vaccine target/diagnostic target is isolated within the clone. Therefore, one of skill in the art would understand what is claimed when the claim is read in light of the specification.

The second issue mentioned by the office is that "method step a has [a] statement that appear[s] to be 'product-by-process' limitation regarding the reagents ustilized (i.e. cell or cellular extracts of the microbe or pathogen 'that have been grown *in vitro*')". The Office alleges that "it is not clear if method steps regarding production of the cell or cellular extracts are required by the claims or not." A product-by-process claim, which is a product claim that defines the claimed product in terms of the process by which it is made, is proper. *In re Luck,* 476 F.2d 650 (CCPA 1973); *In re Pilkington,* 411 F.2d 1345 (CCPA 1969); *In re Steppan,* 394 F.2d 1013 (CCPA 1967). The instant claims are method claims and therefore, not product-by-process claims. The limitation "cells or cellular extracts of the microbe or pathogen that have been grown *in vitro"* is a definite limitation that one of skill in the art would understand in light of the specification. The specification teaches:

> Preferably, a sample containing antibodies against antigens that are expressed by the microbe *in vivo* and *in vitro*, such as a serum sample of an infected host, are contacted with *in vitro* grown whole cells, cell extracts or both of the microbe, or whole cells, extracts of whole cells, or both of cells that are infected with the microbe of interest, *e.g.* a prokaryotic or eukaryotic cell infected with a virus or parasite. . . . The adsorbtion step can be performed by, for example, contacting the antibody sample with whole cells and/or cell extracts that are immobilized on a solid support, such as a nitrocellulose membrane. *See,* Brady & Daphtary, *J. Infect. Dis.* 158:965-972 (1988). Optionally, the whole cell and/or cell extract sample can be denatured before use to expose additional

immunoreactive epitopes. Several successive adsorbtions can be performed using the same or different adsorbtion methodologies.

See page 12, line 17 through page 13, line 8. Also, the specification provides a working example of the claimed methods, which demonstrates use of "cells or cellular extracts of the microbe or pathogen that have been grown *in vitro.*"

> Antibodies in the pooled serum that were reactive with proteins made by *Aa* HK1651 during *in vitro* cultivation were eliminated by repeated adsorbtions using the methods of Brady *et al., J. Infect. Dis*. 158:965-972 (1988). Adsorbtions were performed using both whole cells and cell extracts immobilized on nitrocellulose. Briefly, 500 µl of the pooled sera were subjected to five successive adsorbtions against *in vitro* grown whole cells of *Aa* strain HK1651. The cells were grown in BHI broth at 37°C in ambient atmosphere enriched with 5% CO_2. Each adsorbtion consisted of an overnight incubation of the pooled sera with approximately 10^{11} bacteria in 100 µl phosphate buffered saline (PBS, pH 7.2) containing 0.02% sodium azide with mild agitation at 4°C. The serum was further adsorbed by incubation overnight at 4°C with a nitrocellulose membrane (10 cm diameter) saturated with HK1651 extracts prepared by French-press treatment of 10^{11} *in vitro* grown *Aa* cells. A final adsorbtion step was carried out using the same extract which was heat denatured in a boiling water bath (10 min.) before immobilization on nitrocellulose in order to expose additional immunoreactive epitopes.

See page 28, line 20 through page 29, line 9. Therefore, one of skill in the art would understand that "cells or cellular extracts of the microbe or pathogen that have been grown *in vitro*" is a particular reagent that can be easily made or obtained by one of skilled in the art according to the teachings of the specification.

Applicants respectfully request the withdrawal of the rejection.

Provisional Rejection of Claims 1-5, 7-10, 18 and 19 on the Ground of Nonstatutory Obviousness-Type Double Patenting

Claims 1-5, 7-10, 18 and 19 stand as provisionally rejected the ground of nonstatutory obviousness-type double patenting over claims 1-16 of copending application 12/327,056.

Applicants note that this rejection is not ripe because neither of the applications has been allowed. The Office, however, states that the claims of the

instant invention and those in U.S. Ser. No. 12/327,056 are not patently distinct because "both the presently claimed inventions the inventions as claimed in U.S. applicant 12/327,056 are drawn to methods of isolating a polynucleotide from a microbe utilizing antibodies and antigens." Applicants note that the method steps of the claims in the two applications are different and are indeed patently distinct.

Applicants respectfully request withdrawal of the rejection.

Respectfully submitted,

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